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## **In vitro fertilisation was associated with refractive errors when children reached the age of 11**

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The primary formation of the eye in the human embryo takes place between weeks three and 10, when the eye expresses oestradiol and progesterone receptors in multiple ocular structures (1).

After *in vitro* fertilisation with controlled ovarian hyperstimulation, serum progesterone and oestradiol concentrations are higher than in natural pregnancies up to week six of embryonic development (2). This could imply that these offspring are vulnerable to altered ophthalmic development. Tornqvist et al studied 24,628 children born by IVF between 1985-2005 and reported that the odds ratio for severe visual impairment was 1.65 compared to the general Swedish population (3). However, the underlying mechanisms are unclear. This brief report assessed visual acuity in 11-year-old singletons enrolled in the prospective, assessor-blinded, Groningen ART study, which focused on the possible effects of controlled ovarian hyperstimulation and the *in vitro* culture on children's visual acuity.

Couples who conceived after IVF or naturally while waiting for fertility treatment at the University Medical Center Groningen, the Netherlands, were approached during the third trimester. All had term dates between 1 March 2005 and 31 December 2006. The study comprised three groups of singletons: 48 born after controlled ovarian hyperstimulation IVF, 41 born after modified natural cycle IVF, where only minimal ovarian stimulation was applied, and 60 conceived naturally by

subfertile couples after one year of unprotected intercourse (4). Comparing the two IVF methods enabled us to demonstrate the effect of hyperstimulation and including natural conception enabled us to demonstrate the effect of IVF. Multiple births and cases involving oocyte cryopreservation and oocyte or embryo donation were excluded.

Socioeconomic, prenatal, perinatal and neonatal data were collected two weeks after expected delivery and in 2017, the parents completed a postal questionnaire on the visual acuity of their 11-year-old children and themselves. Data were obtained from the family's ophthalmologist and interpreted by the study's ophthalmologist (MHe), who assessed the appropriateness of glasses, as some children wore glasses without medical indications.

Univariable and multivariable logistic regression were used to estimate differences in background and outcome characteristics. The multivariable logistic regression analyses were adjusted for various confounders: maternal age, preterm birth and time to pregnancy, which were selected on a-priori basis, based on the literature. The results are expressed as odd ratios with 95% confidence intervals and the analyses were performed with SPSS Statistics 20.0 (IBM Corp, New York, USA).

The outcomes of the groups are summarised in Table I and the characteristics of the parents and children are summarised in Table S1. Parental age, gestational age and birth weight were all highest when children were conceived naturally. Time to pregnancy was longest in controlled ovarian hyperstimulation IVF. The headline outcome was that children born after controlled ovarian hyperstimulation IVF were more likely to wear glasses at 11 years of age (23%) and that the rate in the modified IVF and natural subfertile groups were closer to the 11% in the general population. This may have been due to hyperstimulation and could be rectified by supraphysiological levels of oestradiol and progesterone in early pregnancy when the embryonic eye is expressing oestradiol and progesterone receptors.

Toro et al's systematic review, published in 2019, reported that existing studies could not reach conclusions about IVF and visual acuity, as they were too small to and lacked perinatal data

(5). The main strengths of our study were the prospective design and the obstetric, perinatal and ophthalmological data. The study's main limitation was its size, as it was powered to evaluate the participants' neurological development, not their visual acuity. *Post-hoc* analyses indicated that our study was not powered to detect differences in refractory errors or wearing glasses for medical reasons and a chance finding cannot be excluded. In addition, postnatal attrition was 31%. Although the background characteristics of the participants and the non-participants were similar (data not shown), non-response bias was possible.

In conclusion, our findings support the hypothesis that using controlled ovarian hyperstimulation IVF was associated with refractive errors in 11-year-old children. Well-powered follow-up studies on visual acuity are needed so that a meta-analysis can be carried out.

#### **ABBREVIATION**

**IVF, in-vitro fertilisation**

#### **FUNDING**

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#### **CONFLICTS OF INTEREST**

None.

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**Table 1. Ophthalmic outcome measures in the three groups.**

	Group 1 Controlled ovarian hyperstimulation IVF (n = 48)	Group 2 Modified natural cycle IVF (n = 41)	Group 3 Natural conception subfertile (n = 60)
Glasses for medical indications, n (%)	11 (23)	5 (12)	5 (8)
Age started wearing glasses in years, median (range)	6.0 (2.0-10.9)	6.8 (3.7-10.4)	8.8 (3.8-11.2)
Myopia, n (%)	4 (8)	4 (10)	2 (3)
Binocular, n (%)	4 (8)	4 (10)	2 (3)
Sphere (dioptre), median (range)	1.82 (1.25-3.88)	1.63 (1.50-1.75)	2.88 (1.88-3.88)
Cylinder (dioptre), median (range)	NA	NA	NA
Hyperopia, n (%)	5 (10)	2 (5)	3 (5)
Binocular, n (%)	3 (6)	2 (5)	3 (5)
Sphere (dioptre), median (range)	1.25 (0.63-4.63)	1.07 (1.00-1.13)	3.25 (1.75-5.75)
Cylinder (dioptre), median (range)	NA	NA	NA
Astigmatism, n (%)	NA	1 (2)	NA
Astigmatism (dioptre), median (range)	NA	1.50 (0.75-2.25)	NA
Severe ophthalmic impairment, n (%)	0 (0)	0 (0)	1 (2)
One eye blind, n (%)	0 (0)	0 (0)	1 (2)
Congenital abnormalities, n (%)	0 (0)	0 (0)	0 (0)
Minor ophthalmic impairment, n (%)	4 (8)	3 (7)	3 (5)
Strabismus, n (%)	2 (4)	1 (2)	2 (3)
Amblyopia, n (%)	4 (8)	2 (5)	1 (2)

NA, not available.